REMARKS

Applicant respectfully requests reconsideration. Claims 149-166 were previously pending in this application, with claims 161-164 being withdrawn. Claims 149, 153, 157, and 159 are amended herein to clarify the acronyms. Withdrawn claims 161-164 have been canceled. As a result, claims 149-160, 165 and 166 are still pending for examination with claims 149, 157, 165 and 166 being independent claims. No new matter has been added.

For the record, Applicant notes that the Office Action is marked "Final" in the Office Action Summary, while the Detailed Action indicates under Item 4 that the Office Action is "Non-Final". Additionally in a telephone call on August 4, 2008 with Applicant's undersigned representative, the Examiner confirmed that the action was a Non-final Office Action and that the records would be updated to reflect the non-finality of the action.

Rejection Under 35 U.S.C. 103

Claims 149-153 and 155-159 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber et al. (U.S. Patent 5,589,330 December 31, 1996) in view of Saiki et al. (WO 89/11548 November 30, 1989) and Cheung et al. (Proceedings National Academy Science 1996 Vol. 93 p. 14676). According to the Examiner, Shuber et al. teaches a reduced complexity genome (RCG) and methods for detecting the presence or absence of SNP alleles in the native RCG using ASO probes. In addition, according to the Examiner, Saiki et al. teaches a hybridization assay in which oligonucleotides (ASO) probes are attached to a solid support. Further, according to the Examiner, neither Shuber et al., nor Saiki et al. teaches a method using randomly primed PCR to produce the RCG. Also, according to the Examiner, Cheung et al. teaches preparing a randomly primed PCR-derived reduced complexity genome with at least one primer. Finally, according to the Examiner, it would have been obvious to a person of ordinary skill in the art to combine the teachings of Shuber et al., Saiki et al. and Cheung et al. to arrive at the claimed invention.

In the Office Action the Examiner dismissed Applicant's arguments because the Examiner 1) disagrees with the arguments that Shuber et al does not describe a reduced complexity genome, 2) states that the limitation of the RCG being less than 20% of the genomic DNA is unclear and is

"inherent" because the prior art uses a random primer and 3) that the DOP-PCR method of Shuber et al could be used to make genome fragments that are hybridized with the ASO probes of Shuber et al. Applicant addresses each of these points herein.

Shuber et al does not describe a reduced complexity genome (RCG). According to Shuber et al, the target DNA is extracted from a tissue and used without further manipulation or "specific DNA regions" within the DNA are amplified. (Col. 4, lines 10-20). Thus, the DNA of Shuber et al may take one of two forms. It may be a complete genome or it may be a complete genome with several specific sequences having been amplified and included within the mixture. (Col. 4, lines 10-20, Example 1C). Shuber et al does not teach that a subset or fraction of a genome should be used for analysis. In either circumstance, the whole genome is included within the DNA sample of Shuber et al. A RCG is a reproducible fraction of an isolated genome. "The term 'reproducible fraction' refers to a portion of the genome which encompasses less than the entire native genome." (page 16, lines 24-25). A fraction is less than the total genome. It does not include a whole genome, as taught in Shuber et al. For that reason alone Shuber et al does not describe a RCG. In addition to the definition of RCG, claim 149 includes the limitation that the RCG contains less than 20% of the genome. This limitation is discussed in more detail below. However, the limitation confirms that the RCG is not a whole genome.

One reason presented in the Office Action for maintaining the rejection of record is that the limitation of the RCG being less than 20% of the genomic DNA is unclear. Specifically it is stated that the

> "claim does not recite rather the 'wherein the RCG contains less than 20% of genomic material present in a whole genome' limitation is before the reaction, after the reaction, or a ratio of RCG/genomic DNA at any point. The claim does not clearly recite rather only 20% is amplified or less than 20% is amplified." (Office Action Page 8)

The phrase "wherein the RCG contains less than 20% of genomic material present in a whole genome" describes a structural limitation of the RCG rather than a process step in the preparation of a RCG. The claim recites a step for preparing the RCG and then states that the RCG has less than 20% of genomic material present in a whole genome. The plain language of the limitation is clear. The RCG that is produced has less than 20% of the genomic DNA from which it was derived.

Before the RCG is produced it is not a RCG. The claim does not need to recite that only 20% of the genome is amplified.

It is further stated in the Office Action that the limitation of the RCG being less than 20% of the genomic DNA is "inherent" because the prior art of "Shuber et al, Saiki et al and Cheung et al uses a random primer." Neither Shuber et al nor Saiki et al describe the use of a random primer. Thus, a RCG is not inherent in either the Shuber et al or Saiki et al method. Cheung et al. does describe the use of a random primer to prepare the DNA. However, as stated in Applicant's prior response to Office Action, a skilled artisan would not have combined Cheung et al. with Shuber et al in a manner that would produce the claimed invention, regardless of whether Cheung et al describes a RCG. These arguments are presented in further detail below.

Applicants arguments that the combination of Cheung et al and Shuber et al do not produce the claimed invention are dismissed because, according to the Examiner, "DOP-PCR is used to produce fragments of the whole genome for genotyping (abstract). Therefore, the DOP-PCR primers used by Cheung et al. makes fragments of the whole genome." For purposes of clarity Applicant reproduces the entire Abstract of Cheung et al below. It is not clear to Applicant where in the Abstract Cheung et al describe the preparation of genomic fragments that are the equivalent of a RCG having less than 20% of genomic material present in the whole genome.

> "Genetic analysis of limiting quantities of genomic DNA play an important role in DNA forensics, paleoarcheology, genetic disease diagnosis, genetic linkage analysis, and genetic diversity studies. We have tested the ability of degenerate oligonucleotide primed polymerase chain reaction (DOP-PCR) to amplify picogram quantities of human genomic DNA for the purpose of increasing the amount of template for genotyping with microsatellite repeat markers. DNA was uniformly amplified at a large number of typable loci throughout the human genome with starting template DNAs from as little as 15 pg to as much as 400 ng. A much greater-fold enrichment was seen for the smaller genomic DOP-PCRs. All markers tested were amplified from starting genomic DNAs in the range of 0.6-40 ng with amplifications of 200- to 600-fold. The DOP-PCR-amplified genomic DNA was an excellent and reliable template for genotyping with microsatellites, which give distinct bands with no increase in stutter artifact on di-, tri-, and tetranucleotide repeats. There appears to be equal amplification of genomic DNA from 55 of 55 tested discrete microsatellites implying near complete coverage of the human genome. Thus, DOP-PCR appears to allow unbiased, hundreds-fold whole genome amplification of human genomic DNA for genotypic analysis."

Further one of skill in the art would not combine the Shuber et al method with the Cheung et al method because they are incompatible without the further teachings of the invention. Cheung et al is a method for genotyping by preparing DNA using DOP-PCR and then analyzing the DNA using microsatellite repeat markers. Shuber et al. teaches high-throughput screening methods for detecting genetic alterations. As part of the method the target DNA may be amplified by PCR. In particular, Shuber et al. states "one or more *specific* DNA regions present in the target DNA may be amplified by PCR. In this case, the amplified regions are *specified* by the choice of particular flanking sequences for use as primers. Amplification at this step provides the advantage of increasing the concentration of *specific DNA sequences within the target DNA sequence population*." Thus, the teachings of Shuber et al. pertain to the amplification of *specific* regions within the target DNA followed by analysis of those specific sequences using ASOs. One of skill in the art would not have used Cheung's method of analyzing DNA in Shuber's method of ASO hybridization because the skilled artisan would not know which ASOs to analyze in Cheung's sample, since Cheung's sample does not include every sequence within the genome. If the skilled artisan performed a hybridization of Cheung's DNA and did not receive a signal it would be impossible to determine whether the negative result was due to the lack of the SNP in the DNA or simply the DNA not having been amplified using the DOP-PCR method of Cheung et al. Thus, the two methods are not compatible and the skilled artisan would not have combined them. Thus, the combination of references does not produce the claimed invention.

Claims 157-159 have been rejected under 35. U.S.C. 103(a) as being unpatentable over Shuber et al. (U.S. Patent 5,589,330 December 31, 1996) in view of Saiki et al. (WO 89/11548 November 30, 1989) and Cheung et al. (Proceedings National Academy Science 1996 Vol. 93 p. 14676) as applied to Claims 149-153 and 155-156 and in view of Hoffman et al. (American Journal of Medical Genetics 1998 Vol. 80 p. 140).

The Examiner has dismissed Applicants arguments that the combination of Shuber et al, Saiki et al and Cheung et al did not produce the claimed invention. Applicant traverses the maintenance of the rejection for each of the reasons presented above. However, the Examiner has not addressed Applicant's point that Hoffman et al was published after Applicant's priority date.

Thus, Hoffman et al is not prior art against the claims. For that reason alone, the rejection of claims 157-159 should be dropped. Hoffman et al was not prior art to the claimed invention and it was critical to the rejection. It is requested that the rejection be withdrawn.

Claims 165 and 166 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber et al. (U.S. Patent 5,589,330 December 31, 1996) in view of Cheung et al. (Proceedings National Academy Science 1996 Vol. 93 p. 14676).

The Examiner has dismissed Applicant's arguments that the combination of Shuber et al and Cheung et al did not produce the claimed invention. In particular the Examiner states that Shuber et al describes a RCG and that the combination of references teach a randomly primed PCR RCG. Applicant traverses the maintenance of the rejection for each of the reasons presented above.

Specifically, Shuber et al does not describe a reduced complexity genome (RCG) and one of skill in the art would not have used the DOP-PCR method described in Cheung et al in the methods of Shuber et al. As stated in detail above, according to Shuber et al, the target DNA is extracted from a tissue and used without further manipulation or "specific DNA regions" within the DNA are amplified. (Col. 4, lines 10-20). Thus, the DNA of Shuber et al may take one of two forms. It may be a complete genome or it may be a complete genome with several specific sequences having been amplified and included within the mixture. (Col. 4, lines 10-20, Example 1C). Shuber et al does not teach that a subset or fraction of a genome should be used for analysis. A RCG is a reproducible fraction of an isolated genome. It does not include a whole genome, as taught in Shuber et al. For that reason alone Shuber et al does not describe a RCG.

Further, one of skill in the art would not have combined the Shuber et al method with the Cheung et al method because they are incompatible without the further teachings of the invention. Cheung et al is a method for genotyping by preparing DNA using DOP-PCR and then analyzing the DNA using microsatellite repeat markers. In the method of Cheung et al one does not need to know the identity of the DNA that has been amplified in order to analyze the genotype. Shuber et al analyzes whole DNA, optionally including specific sequences that have been amplified by PCR, using ASOs. Shuber et al must know in advance whether a specific region of DNA is present in his sample before performing the method. Since the whole genome is present in Shuber's mixture, this

is not an issue. One of skill in the art would not have used Cheung's DNA sample in Shuber's method of ASO hybridization because the skilled artisan would not know which ASOs to analyze in Cheung's sample, since Cheung's sample does not include every sequence within the genome. If the skilled artisan performed a hybridization of Cheung's DNA and did not receive a signal it would be impossible to determine whether the negative result was due to the lack of the SNP in the DNA or simply the DNA not having been amplified using the DOP-PCR method of Cheung et al. Thus, the two methods are not compatible and the skilled artisan would not have combined them.

Even if one skilled in the art combined the DNA sample of Cheung et al with the method of Shuber et al the combination would not produce all of the elements of claim 165 in the absence of the teachings of the instant invention. Claim 165 requires that the hybridization pattern of the RCG determine the presence or absence of SNP alleles. If a skilled artisan were to use Cheung's DNA in Shuber's method of ASO hybridization one could not definitively state that the absence of a signal was due to the absence of the SNP in the genome. This is because Cheung's DNA sample does not include the whole genome. If an ASO was used that was representative of a DNA fragment that was not present in Cheung's sample then a negative signal would be achieved, but, it would not be indicative of the absence of the SNP in the genome. Thus, if the skilled artisan performed a hybridization of Cheung's DNA and did not receive a signal it would be impossible to determine whether the negative result was due to the lack of the SNP in the DNA or simply the DNA not having been amplified using the DOP-PCR method of Cheung et al.

Claims 149 and 154-156 have been rejected under 35. U.S.C. 103(a) as being unpatentable over Shuber et al. (U.S. Patent 5,589,330 December 31, 1996) in view of Saiki et al. (WO 89/11548 November 30, 1989) and in view of Drmanac et al. (U.S. Patent 6,297,006 October 2, 2001).

In the Office Action the Examiner dismissed Applicants arguments because the Examiner A) disagrees with Applicants arguments that Shuber et al does not describe a reduced complexity genome and B) does not agree with Applicants arguments against the motivation for combining references. Applicants address each of these points herein.

A) The issue of whether Shuber et al discloses a RCG is discussed extensively above. Rather than repeating such arguments again, Applicant requests that the Examiner reconsider each of those points here. Shuber et al does not describe a RCG.

B) The Examiner had previously cited 2 potential motivations for combining the references. Applicants disagreed with both and presented arguments that one of skill in the art would not have been motivated to combine Shuber et al with Dramanac et al in the manner suggested by the Examiner. Specifically Applicant presented the following arguments:

1. The motivation provided in the Office Action:"The ordinary artisan would have been motivated to modify the method of Shuber et al. and Saiki et al. to produce the RCG fragments using adapter PCR (randomly primed PCR derived RCGs) as taught by Drmanac et al. because Drmanac et al. teaches that by using a small number of adapters a million different fragments may be specifically amplified in identical conditions." (Office Action page 26-27). Shuber teaches that PCR amplification can be used to increase "the concentration of specific DNA sequences within the target DNA sequence population." (Col. 4 lines 15-18). Using PCR to amplify a million different fragments would have been contrary to the stated purpose of Shuber, to selectively increase the concentration of specific sequences.

2. The motivation provided in the Office Action: "The ordinary artisan would be motivated to produce RCGs with adapter PCR, because Drmanac et al teaches that DNA differences between several patients can be analyzed and that this approach eliminates the need fro expensive genetic mapping on extensive pedigrees." (Office Action page 27). One of skill in the art would not have been motivated by this teaching in Drmanac et al to combine it with the hybridization method of Shuber, because this combination would raise the complexity issues that Drmanac et al seeks to avoid. The ease of analysis is achieved by Drmanac through sequencing. Drmanac states that the technique is of "special value when there is no such genetic data or material." (Col. 51 lines 22-23). Shuber teaches that the DNA is hybridized to oligonucleotides, "wherein each oligonucleotide comprises a variant of a known sequences in the DNA samples." (Col.. 2 lines 10-13). Thus, one of skill in the art would not have taken the Drmanac material and put it into the methods of Shuber, which requires knowledge of genetic data for generation of the ASOs used in the hybridization step.

1) In response to Applicant's arguments it is stated that it would have been obvious for the skilled artisan "to modify the method of Shuber et al. to incorporate adapter primers into the method step of PCR in order to amplify fragments in identical conditions" and that Drmanac et al does not imply that all the fragments are produced at the same time. (Office Action page 21) Firstly,

Applicant notes that the point of the argument was that one of skill in the art would not have been motivated to use the adapter primer of Drmanac et al in the method of Shuber et al because of inconsistent teachings in the references. The issue of the motivation is not addressed specifically in the Office Action. The point that Drmanac et al is making is that adapter PCR allows them to amplify many different sequences at one time. By using adapter PCR they are not limited to amplifying specific sequences. That is why Drmanac et al produces millions of fragments. Shuber et al. teaches a method in which "one or more *specific* DNA regions present in the target DNA may be amplified by PCR. The teachings of Shuber et al. pertain to the amplification of *specific* regions within the target DNA followed by analysis of those specific sequences using ASOs. One of skill in the art would not have used Drmanac's method of amplifying DNA in Shuber's method of ASO hybridization because the skilled artisan would not know which ASOs to analyze in Drmanac's sample. When Shuber et al is trying to identify the presence or absence of a SNP allele in a DNA sample Shuber et al needs to know in advance that the DNA corresponding to the SNP is present in the sample. Shuber et al achieves this by using whole genomes and or amplifying specific sequences that he will then analyze. By using Drmanac's amplification method, Shuber et al would not be able to determine whether the DNA corresponding to the SNP is present in the sample, since Drmanac's method would produce an unknown subset of the genome. One skilled in the art would have no motivation to replace Shuber's genomic sample with that taught by Drmanac et al because it would be non-functional in the absence of the teachings of the instant invention. Thus, the two methods are not compatible and the skilled artisan would not have combined them.

Secondly, even if the skilled artisan were to combine the method of Shuber et al with the amplified DNA of Drmanac et al they would not be able to determine the presence or absence of the SNP allele, an important limitation of claim 149. Claim 149 requires that the presence or absence of a SNP allele be determined by the hybridization with an ASO probe. If a skilled artisan were to use Drmanac's DNA in Shuber's method of ASO hybridization one could not definitively state that the absence of a signal was due to the absence of the SNP in the genome. This is because Drmanac's DNA sample does not include the whole genome. If an ASO was used that was representative of a DNA fragment not present in Drmanac's sample then a negative signal would be achieved but it would not be indicative of the absence of the SNP in the genome. Thus, if the skilled artisan

performed a hybridization of Drmanac's DNA and did not receive a signal it would be impossible, based solely on the hybridization reaction, to determine whether the negative result was due to the lack of the SNP in the DNA or simply the DNA not having been amplified using the adapter-PCR method of Drmanac et al. Thus, the combination does not produce the claimed invention in the absence of the teachings of the instant invention.

2) In response to Applicant's arguments it is argued that the sequencing step of Drmanac et al would not be combined with the method of Shuber et al, just the adapter PCR method would be combined with Shuber's method. This statement does not address the deficiencies with the motivation to combine. Rather it simply concludes that the references would be combined in a certain way. The point that Applicant is presenting is that one of skill in the art would not have been motivated by the teachings in Drmanac et al to combine it with the hybridization method of Shuber et al.

Merely finding two references that together teach each of the limitations of the claims is not enough to prove obviousness. In such a circumstance, some reason, i.e., a suggestion or motivation, from the prior art for combining the teachings of the references also must be found.[1] Such a suggestion or motivation may come from the references themselves, from knowledge or common sense of those skilled in the art, such as knowledge that certain references are of special interest in a field, or even from the nature of the problem to be solved.[2] The range of sources available does not diminish the requirement for actual clear and convincing evidence of the source of the suggestion or motivation.[3] However, as stated by the Supreme Court, "the combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable

[1] In re Denis Rouffet et al., 149 F.3d 1350, 1355-56, 47 U.S.P.Q.2d 1453, 1149 (Fed. Cir. 1998).

[2] Smiths Industries Medical Systems, Inc. v. Vital Signs, Inc., 183 F.3d 1347, 51 U.S.P.Q.2d 1415 (Fed. Cir. 1999), *citing* In re Rouffet, 149 F.3d 1350, 1355-56, 47 U.S.P.Q.2d 1453, 1149 (Fed. Cir. 1998); Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc., F.3d 1568, 1573, 37 U.S.P.Q.2d 1626, 1630 (Fed. Cir. 1996).

[3] C.R. Bard v. M3 Sys, Inc., 157 F.3d 1340, 1352 (Fed. Cir. 1998). See also Smith Industries, supra and In re Dembiczak, supra.

results – a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions."[4]

In the instant case, the combination of references is not merely a combination of familiar elements according to known methods that does no more than yield predictable results. The DNA sample of Drmanac et al is quite different than that of Shuber et al. One cannot simply be replaced with the other without a further reason or motivation. A motivation to combine is required. The original motivation provided for the combination was that Drmanac et al teaches that the DNA of different patients can be analyzed without the need for expensing mapping technology. However, the use of Shuber's methods with Drmanac's DNA sample would raise the complexity issues that Drmanac et al seeks to avoid. Thus the motivation is improper. The ease of analysis is achieved by Drmanac et al through sequencing. Drmanac et al states that the technique is of "special value when there is no such genetic data or material." (Col. 51 lines 22-23). Shuber et al teaches that the DNA is hybridized to oligonucleotides, "wherein each oligonucleotide comprises a variant of a known sequences in the DNA samples." (Col. 2 lines 10-13). Thus, one of skill in the art would not have taken the Drmanac et al material and put it into the methods of Shuber et al, which requires knowledge of genetic data for generation of the ASOs used in the hybridization step. Thus, one of skill in the art would not have been motivated to combine the references as suggested by the examiner.

Claims 157 and 160 have been rejected under 35. U.S.C. 103(a) as being unpatentable over Shuber et al. (U.S. Patent 5,589,330 December 31, 1996) in view of Saiki et al. (WO 89/11548 November 30, 1989), Dramanc et al. (U.S. Patent 6,297,006 October 2, 2001), and in view of Hoffman et al. (American Journal of Medical Genetics 1998 Vol. 80 p. 140.

The Examiner has dismissed Applicants arguments that the combination of Shuber et al, Saiki et al and Dramanc et al did not produce the claimed invention. Applicant traverses the maintenance of the rejection for each of the reasons presented above. However, the Examiner has not addressed Applicant's point that Hoffman et al was published after Applicant's priority date.

[4] KSR International Co. v. Teleflex, Inc., 127 S. Ct. 1727, 1740-41, 82 USPQ2d 1385, 1396 (2007).

Thus, Hoffman et al is not prior art against the claims. For that reason alone, the rejection should be dropped. It is requested that the rejection be withdrawn.

Double Patenting Rejection

Claims 149-160 and 165-166 have been rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-27 of U.S. Patent No. 6,703,228.

Applicant will forward a terminal disclaimer under separate cover prior to allowance of the claims.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, the Director is hereby authorized to charge any deficiency or credit any overpayment in the fees filed, asserted to be filed or which should have been filed herewith to our Deposit Account No. 23/2825, under Docket No. M0656.70098US00.

Dated: August 5, 2008

Respectfully submitted,

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